CLAIMS

What is claimed is:

1. A method of screening a drug candidate for a selected pharmacological activity, said method comprising:

(a) selecting a receptor that demonstrates a perturbation of conformation when bound to a selected ligand, wherein said selected ligand is identified with the selected pharmacological activity;

(b) generating a hydrogen exchange profile of the receptor;

(c) generating a hydrogen exchange profile of a first receptor complex comprising the receptor bound to said selected ligand;

(d) defining a first perturbation of the receptor conformation, which perturbation is induced by binding of the receptor to the selected ligand;

(e) generating a hydrogen exchange profile of a second receptor complex comprising the receptor bound to said drug candidate;

(f) defining a second perturbation of the receptor conformation which perturbation is induced by binding of the receptor to the drug candidate; and

(g) comparing the first perturbation to the second perturbation, the similarity between the two perturbations of the receptor conformation being predictive of the drug candidate having the selected pharmacological activity.

2. The method according to claim 1 wherein the drug candidate screened in the screening method is selected by computer-assisted modeling of the selected receptor.

3. The method according to claim 1 wherein said computer-assisted modeling comprises:

(a) modeling a binding interaction of at least one compound with the receptor to identify at least one potential receptor ligand; and

(b) selecting at least one potential receptor ligand as a drug candidate.

4. The method according to claim 1 wherein said computer-assisted modeling comprises:

(a) predicting at least one hydrogen exchange profile of the selected receptor bound to at least one potential drug candidate by modeling probable conformational states of the receptor bound to the at least one potential drug candidate;

(b) defining at least one conformational perturbation of the receptor predicted to be induced by binding of the receptor to the at least one potential drug candidate; and

(c) selecting a drug candidate wherein the predicted conformational perturbation is similar to a conformational perturbation of the receptor induced by binding of the receptor to a selected ligand, which selected ligand is identified with a selected pharmacological activity.

5. The method according to claim 1 wherein defining the first perturbation comprises calculating the difference between the hydrogen exchange profile of the receptor and the hydrogen exchange profile of the receptor bound to the selected ligand.

6. The method according to claim 1 wherein defining the second perturbation comprises calculating the difference between the hydrogen exchange profile of the receptor and the hydrogen exchange profile of the receptor bound to the drug candidate.

7. The method according to claim 2 wherein the selected receptor is a nuclear receptor.

8. The method according to claim 7, wherein the nuclear receptor is selected from the group consisting of glucocorticoid receptor, estrogen receptor, peroxisome proliferator-activated receptor, vitamin D receptor, liver X receptor and retinoic X receptor.

9. The method according to claim 2 wherein the selected receptor is a kinase.

10. The method according to claim 9 wherein the kinase is selected from the group consisting of c-JUN *N*-terminal kinase, glucokinase and protein tyrosine phosphatase 1b.

11. The method according to claim 2 wherein the selected receptor is a G-protein coupled receptor.

12. The method according to claim 11 wherein the G-protein coupled receptor is an AMPA receptor,

13. The method according to claim 2 wherein the selected receptor is a transcription factor other than a nuclear receptor.

14. The method according to claim 13 wherein the transcription factor is selected from the group consisting of TFIIA, TFIIB, TFIIC, TFIID, TFIIE, TFIIF, TFIIH, TFIIK (CTD kinase), TATA binding protein, RelA, RelB, p50/p105, p52/p100, X-Rel2, and NF-kB.

15. The method according to claim 2, wherein the step of generating a hydrogen exchange profile comprises determining the quantity of isotopic hydrogen or the rate of hydrogen exchange, or both the quantity of isotopic hydrogen and the rate of hydrogen exchange, of a plurality of peptide amide

hydrogens exchanged for said isotopic hydrogen in a receptor or receptor complex that is hydrogen-exchanged with a hydrogen isotope other than ^{1}H.

16. The method according to claim 15, wherein the step of determining the quantity of isotopic hydrogen or the rate of hydrogen exchange, or both the quantity of isotopic hydrogen and the rate of hydrogen exchange, comprises the steps of:

(a) contacting the selected receptor or receptor complex with an isotopic hydrogen exchange reagent for a selected time interval to form a isotopic hydrogen-exchanged receptor or receptor complex;

(b) under slow hydrogen exchange conditions, progressively degrading the isotopic hydrogen-exchanged receptor or receptor complex to obtain a series of sequence-overlapping peptide fragments;

(c) measuring the amount of isotopic hydrogen contained in each peptide fragment; and

(d) correlating the amount of isotopic hydrogen contained in each peptide fragment with an amino acid sequence of the receptor or receptor complex from which the peptide fragment was generated, thereby determining the quantity of isotopic hydrogen or the rate of hydrogen exchange, or both the quantity of isotopic hydrogen and the rate of hydrogen exchange, of a plurality of peptide amide hydrogens exchanged for isotopic hydrogen in the receptor or receptor complex.

17. The method according to Claim 16 in which said progressively degrading comprises contacting the isotopic hydrogen-exchanged receptor with an acid-stable endopeptidase under slow hydrogen exchange conditions.

18. The method according to claim 17 wherein the acid-stable endopeptidase is immobilized on a solid-phase support.

19. The method according to claim 18 wherein the acid-stable endopeptidase is selected from the group consisting of pepsin, Newlase, Aspergillus proteases, protease type XIII, and combinations thereof.

20. The method according to claim 16 in which said progressively degrading comprises:

(a) fragmenting the isotopic hydrogen-exchanged receptor into a plurality of peptide fragments under slow hydrogen exchange conditions;

(b) identifying which peptide fragments of said plurality of peptide fragments are isotopic hydrogen-exchanged; and

(c) sequentially terminally degrading the isotopic hydrogen-exchanged peptide fragments under slow hydrogen exchange conditions, to obtain a series of subfragments, wherein each subfragment of the series is composed of from about one to about five fewer amino acid residues than the preceding subfragment in the series.

21. The method according to claim 20 wherein sequentially terminally degrading comprises reaction of the isotopic hydrogen-exchanged peptide fragments with an acid-resistant carboxypeptidase under slow hydrogen exchange conditions.

22. The method according to claim 21 in which said acid-resistant carboxypeptidase is selected from the group consisting of carboxypeptidase P, carboxypeptidase Y, carboxypeptidase W, carboxypeptidase C and combinations thereof.

23. A method according to claim 15 wherein said isotopic hydrogen is deuterium.

24. A method according to claim 23, wherein the presence and quantity of deuterium on said subfragments of the isotopic hydrogen-exchanged receptor is determined by measuring the mass of said subfragments.

25. A method according to claim 24, wherein said measuring is performed using mass spectrometry.

26. A method according to claim 15 further comprising the use of conditions that effect protein denaturation under slow hydrogen exchange conditions prior to generation of said fragments.

27. A method according to claim 15 further comprising disrupting disulfide bonds in the isotopic hydrogen-exchanged receptor prior to generating said fragments.

28. A method according to claim 27, wherein said disrupting comprises contacting the isotopic hydrogen-exchanged receptor with a water-soluble phosphine.